UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

September 24, 1998

MEMORANDUM

EPA Reg. No: 1021-RTNU PYROCIDE LIQUID PET SPRAY 7418
DP Barcode: D246641
Case No: 061533

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505C)

Byron T. Backus 9/24/98
JCR

To: Joseph Tavano/Susan Lewis, PM 03
Insecticide Branch
Registration Division (7505C)

Action Requested: Review of two companion (formerly "domestic") animal safety studies, one (dogs) in MRID 44314009 and one (cat) in MRID 44314010.

Comments and Recommendations: The primary reviews were done at Oak Ridge and then were secondarily reviewed in TRB. These secondary reviews were then sent to HED for additional review and comment.

1. With respect to MRID 44314009 "Evaluation of the Potential Dermal and Systemic Toxicity of Permalool Plus Flea and Tick Foam in the Dog" the study has been classified as acceptable by TRB with the comment that the study, as conducted, establishes a 5X safety factor for adult dogs only, since the youngest animal in the study was 27 weeks old.

While the HED Companion Animal Safety Committee recommended that this study should be classified as unacceptable but upgradable upon submission and acceptability of additional information (see the attached memorandum dated 9/22/98), TRB has concluded that there is sufficient information within the study report, and that the study adequately conforms to 870.7200 OPPTS Guidelines. While it might have been helpful to have information relating to the amount of product applied to each animal, the 870.7200 Guidelines do not state that this is necessary information under any circumstances. As to the question of individual animal data in the report, the reporting adequately indicates a lack of indications of toxicity in the treated animals. TRB concludes the study is acceptable.

2. With respect to MRID 44314010 "Evaluation of the Potential Dermal and Systemic Toxicity of Permalool Plus Flea and Tick Foam in the Cat" the study has been classified as unacceptable, as Elizabethan collars were placed on the animals from all dose groups for 24 hours after treatment, to prevent them from grooming themselves and orally ingesting the material. In addition, even animals in the 1X group had increased incidences of salivation, indicating that a 5X safety factor for this product has not been established even in the absence of ingestion of the test material from grooming.

3. It is noted that neither study included a repeat treatment. This is consistent with the labeling which indicates treatment should be repeated every three months. As noted in the memorandum from the HED Companion Animal Safety Committee, the Guidelines specify that retreatments within a study are not required if the retreatment interval on the label is greater than 30 days. Therefore, these studies would not support products with repeat treatments of less than 30 days.

4. The studies in MRIDs 44314009 and 44314010 utilized a test material with the following actives with their percentages:

057001 N-Octyl bicycloheptene dicarboximide	1.000%
109701 Permethrin	0.195%
069001 Pyrethrins	0.297%
129032 Pyriproxyfen (Nylar)	0.124%
128722 ETOC	0.107%
128838 Linalool	0.112%

The proposed product EPA Reg. No: 1021-RTNU PYROCIDE LIQUID PET SPRAY 7418 has the following actives and percentages:

057001 N-Octyl bicycloheptene dicarboximide	1.000%
069001 Pyrethrins	0.180%
129032 Pyriproxyfen (Nylar)	0.125%

DATA EVALUATION REPORT

Permalool Plus Flea and Tick Foam

STUDY TYPE: Companion Animal Safety – Dog (86-1)

Prepared for

Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer: Cheryl B. Bast, Ph.D., D.A.B.T.	Signature: Date:	Cheryl B Bast 8-20-98
Secondary Reviewers: H. Tim Borges, Ph.D., MT (ASCP), D.A.B.T.	Signature: Date:	H T Borges 8-20-98
Robert H. Ross, M.S., Group Leader	Signature: Date:	Robert H. Ross 8-20-98
Quality Assurance: Lee Ann Wilson, M.A.	Signature: Date:	L. A. Wilson 8-20-98

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Managed by Lockheed Martin Energy Research Corp., for the U.S. Department of Energy under Contract No. DE-AC05-96OR22464.

EPA Reviewer:Byron T. Backus, Ph.D.
Technical Review Branch(7505C)
EPA Work Assignment Manager:
John Redden, M.S.
Registration Division (7505C)

Byron T. Backus Date: 9/24/98

Date: 9/24/98

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety/Dogs [OPPTS 870.7200]

EPA I.D. NUMBERS: DP BARCODE: D246641; MRID NUMBER: 44314009

TEST MATERIAL: Permalool Plus Flea and Tick Foam

STUDY NUMBER: WEL Study No. 96668

TESTING FACILITY: White Eagle Toxicology Laboratories, 2003 Lower State Road, Doylestown, PA 18901

SPONSOR: McLaughlin Gormley King Company, 8810 Tenth Avenue North, Minneapolis, MN 55427-4372

TITLE OF REPORT: Evaluation of the Potential Dermal and Systemic Toxicity of Permalool Plus Flea and Tick Foam in the Dog

AUTHOR: C. Steven Godin

REPORT ISSUED: February 4, 1997

EXECUTIVE SUMMARY: In a domestic animal safety study (MRID 44314009), Permalool Plus Flea and Tick Foam (Active Ingredients: MGK-264: 1.00%; ETOC: 0.0997%; Pyrethrins:0.300%;Nylar:0.125%;Permethrin:0.199%;Linalool: 0.108%)was dermally applied once, three times or five times to groups of 6 male and 6 female beagle dogs. Controls received five applications of a placebo foam. The multiple treatments were applied at 1-hour intervals. Blood samples were obtained on the day prior to and the day following dosing for hematology and clinical chemistry measurements. Animals were observed for 28 days.

No mortality was observed and there were no treatment-related, biologically-significant effects on body weight, clinical biochemistry, or hematology. Sporadic statistically-significant clinical chemistry and hematology effects were observed in male and female dogs in all treatment groups. However, none of the effects are considered toxicologically significant since some effects occurred in control as well as treated animals, no dose-response was observed, and/or measured values were within historical control ranges for dogs.

This study is classified as **acceptable (guideline)** and satisfies the guideline requirements for a domestic animal safety study (86-1) in dogs. A 5X margin of safety was demonstrated. However, it is noted that the label for this product includes specific directions for treatment of puppies over 12 weeks of age, while the youngest dog in this study was 27 weeks old. Therefore, this study supports only the proposed use on adult dogs.

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

I. MATERIALS

A. Test material: Permalool Plus Flea and Tick Foam

Description: Pressurized foam
Lot/Batch No.: LP101996P
Active Ingredients: MGK-264: 1.00%; ETOC: 0.0997%;Pyrethrins:0.300%; Nylar: 0.125%; Permethrin: 0.199%; Linalool: 0.108%;
Storage Conditions: Stored at ambient temperature and humidity

B. Administration: Dermal

C. Vehicle and/or positive control

Vehicle: Permalool Plus Flea and Tick Foam (Placebo)
Positive control: none

D. Test animals

Species: Dog
Breed: Beagle
Age and weight at study initiation: males: 27 to 90 weeks; 8.5-12 kg females: 35 to 68 weeks; 7.1-11.7 kg
Source: White Eagle Laboratories, Inc., Doylestown, PA
Housing: individually in elevated metal cages
Diet: Purina Certified Canine Diet #5007, approx. 400 g/day
Water: *ad libitum*
Environmental conditions:
Temperature: 65-78 °F
Humidity: 22-81%
Acclimation period: 22 days

II. STUDY DESIGN

A. In life dates

Start: October 22, 1996; end: November 21, 1996

B. Animal assignment/ Dosage and Administration

Dogs were randomly distributed within the experimental groups (Table 1) on the basis of body weight using a random permutation table. Groups of 6 dogs/sex were dermally treated with five applications of either placebo; or one application(1X); or 3 applications (3X); or 5 applications (5X) of the test material. If more than one application was made, then applications were at one hour intervals. According to the report text applications were made according to label directions, which state the following:

"Cover animal's eyes with a hand. Do not spray directly on mouth, nose and eyes. Spray head, ears and chest until damp. With finger tips, rub into face, around mouth, nose and eyes. Then spray from the neck to the tail, finishing legs last. For best penetration of spray to skin and on heavily coated animals, direct spray against the natural lay of the hair, spraying the ruffled hair directly behind the hand. Make sure the spray thoroughly wets ticks. [When used on miniature and toy breeds of dogs or on cats, towel dry the animal after ½ hour if not totally dry.]... Avoid contact with genitalia."

Table 1. Experimental Design

Group	No. of animals		Treatment	Number of applications
	Male	Female		
1	6	6	Placebo	5
2	6	6	Test Material	1
3	6	6	Test Material	3
4	6	6	Test Material	5

Data taken from p. 11, MRID 44314009.

C. Dose selection rationale

The rationale for dose levels was to establish the margin of safety and potential dermal and systemic toxicity at 1X, 3X, and 5X the recommended topical application.

D. Experimental design

Clinical observations were conducted hourly for four hours following the final application of test material or placebo and twice daily, thereafter, for 27 days. Effects on skin and fur, eyes and mucous membranes, respiratory system, circulatory system, autonomic and central nervous system, somatomotor activity and behavior pattern were noted. Particular attention was paid to seizures, tremors, salivation, vomiting, and diarrhea. Body weights were recorded pre-test and on days 0, 7, 14, 21, and 28 of the study. Food consumption was measured daily for each animal during the acclima-

tion period and during the study. Food consumption on days -2 and 0 were measured for 6 hour periods due to fasting for clinical chemistry and hematology testing.

E. Pathological parameters

Blood samples were obtained by venipuncture of the jugular vein on Day -1 (pretreatment) and Day 1. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)*
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)*
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)*
x	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)*		
x	(Activated partial thromboplastin time)*		
	Erythrocyte morphology		

*Recommended in 86-1 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium	x	Blood urea nitrogen*
x	Phosphorus*		Total Cholesterol
x	Potassium*	x	Globulin*
x	Sodium*	x	Glucose*
		x	Total and direct bilirubin*
	ENZYMES	x	Total serum protein*
x	Alkaline phosphatase(ALK)*		(TP)
	Cholinesterase(ChE)		Triglycerides
	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)		
x	Serum alanine amino- transferase (also SGPT)*		
x	Serum aspartate amino- transferase(also SGOT)*		
	Gamma glutamyl transferase(GGT)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in 86-1 Guidelines.

F Statistics

Group mean values with standard deviations were calculated from numerical data. Between day comparisons of mean clinical-chemistry and hematology data within each treatment group were done with a paired two-tailed Student's t-test. Body weight and food consumption data were compared using a one-way ANOVA. If significant ($p \leq 0.05$) differences were found, Bonferroni's Multiple Comparison post-test was used to determine statistical significance.

G. Disposition of animals

The dogs were returned to the animal colony at White Eagle Laboratories at the end of the study.

H. Compliance

Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

III. RESULTS

A. Exposure levels

The exact test article exposure concentrations could not be calculated from the information provided. The Flea and Tick Foam was applied according to package directions. The animals were not toweled after treatment so that the test or control material could air dry.

B. Mortality

No dogs died during the study.

C. Clinical signs

Clinical observations are presented in Table 2. Minor gastrointestinal disturbance as indicated by emesis was noted in one placebo control dog and in one dog receiving 1X treatment. One 5X-treated dog exhibited salivation after the third and fifth treatments. None of the effects are considered treatment-related. The emesis was sporadic and occurred only in control and 1X-treated dogs. The salivation was observed in only one animal and only during handling.

TABLE 2*. Clinical observations			
Treatment group	**Sex**	**Day**	**Observation**
5X- Placebo Control	M	12	Large amount of brown, liquid emesis containing food
		21	Moderate amount of brown, liquid/soft emesis containing food
		22	Small amount of yellow, foamy, liquid emesis
1X- Treatment	F	26	Moderate amount of brown, soft emesis containing food
5X- Treatment	M	0	Moderate salivation during 3rd application. Moderate salivation during 5th application. Duration <4 minutes.

Data taken from p. 18, MRID 44314009.

D. Bodyweight and weight gain

No significant differences in group body weight means occurred for animals of either sex at any observation period. The mean body weights of all dogs increased during the acclimation period and decreased during the Day 0 to Day 7 interval after treatment. The decreases did not reach statistical significance and are not considered treatment-related; there was no dose-response and similar decreases were observed in both control and treated animals. The mean body weights increased after Day 7 through the end of the study.

E. Food consumption

No significant difference in food consumption occurred for treated or control animals at any time during the study.

F. Hematology

No treatment-related, biologically-significant hematological effects were observed. Although there were sporadic incidences of statistically significant hematological effects, there was no dose-response and no biological significance since values were generally within normal ranges for dogs.

G. Clinical chemistry

No treatment-related, biologically-significant effects were observed. Although there were sporadic incidences of statistically significant clinical chemistry effects, there was no dose-response and no biological significance since values were generally within normal ranges for dogs.

H. Necropsy findings

No necropsies were performed.

IV. AUTHOR'S CONCLUSIONS

In the report summary (p. 5 of MRID 44314009) it is stated: "There were no test article-related effects noted during the four-week post-dose observation period. Therefore, the test article is considered nontoxic under the conditions of the study."

V. DISCUSSION

Groups of 6 male and 6 female beagles were treated five times with a placebo control foam or once, 3X or 5X at 1-hr. Intervals with Permalool Plus Flea and Tick Foam.

No mortality was observed and there were no treatment-related and/or biologically-significant effects on body weight, clinical biochemistry, or hematology. Sporadic statistically-significant clinical chemistry and hematology effects were observed in male and female dogs in all treatment groups. However, none of the effects are considered toxicologically significant since many effects occurred in control as well as treated animals, no dose-response was observed, and/or measured values were within normal control ranges for dogs.

This study generally followed the pertinent guidelines for a domestic animal safety study (86-1). The required 5X margin of safety has been demonstrated and the study is **acceptable;** however, it is noted that the label for this product includes specific directions for treatment of puppies over 12 weeks of age, while the youngest dog in this study (MRID 44314009) was 27 weeks old. Therefore, this study supports only the proposed use on adult dogs.

DATA EVALUATION REPORT

Permalool Plus Flea and Tick Foam

STUDY TYPE: Companion Animal Safety – CAT (86-1)

Prepared for

Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer:		
Cheryl B. Bast, Ph.D., D.A.B.T.	Signature:	_____
	Date:	_____
Secondary Reviewers:		
H. Tim Borges, Ph.D.,	Signature:	_____
MT (ASCP), D.A.B.T.	Date:	_____
Robert H. Ross, M.S., Group Leader	Signature:	_____
	Date:	_____
Quality Assurance:		
Susan Chang, M.S.	Signature:	_____
	Date:	_____

Disclaimer

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Managed by Lockheed Martin Energy Research Corp., for the U.S. Department of Energy under Contract No. DE-AC05-96OR22464.

EPA Reviewer:Byron T. Backus, Ph.D. Date: 9/24/98
Technical Review Branch (7505C)
EPA Work Assignment Manager:John Redden, M.S. Date: 9/24/98
Registration Division (7505C)

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety/Cats (§86-1) [OPPTS 870.7200]

EPA I.D. NUMBERS: DP BARCODE: D246641; MRID NUMBER: 44314010

TEST MATERIAL: Permalool Plus Flea and Tick Foam

STUDY NUMBER: WEL Study No. 96667

TESTING FACILITY: White Eagle Toxicology Laboratories, 2003 Lower State Road, Doylestown, PA 18901

SPONSOR: McLaughlin Gormley King Company, 8810 Tenth Avenue North, Minneapolis, MN 55427-4372

TITLE OF REPORT: Evaluation of the Potential Dermal and Systemic Toxicity of Permalool Plus Flea and Tick Foam in the Cat

AUTHOR: C. Steven Godin

REPORT ISSUED: April 16, 1997

EXECUTIVE SUMMARY: In a domestic animal safety study (MRID 44314010), Permalool Plus Flea and Tick Foam (Active Ingredients: MGK-264: 1.00%; ETOC: 0.0997%; Pyrethrins: 0.300%;Nylar:0.125%;Permethrin:0.199%;Linalool: 0.108%)was dermally applied once, three times or five times to groups of 6 male and 6 female domestic shorthair cats. Controls received five applications of a placebo foam. The multiple treatments were applied at 1-hour intervals. Blood samples were obtained on the day prior to and the day following dosing for hematology and clinical chemistry measurements. Animals were observed for 28 days.

No mortality was observed. Small to moderate amounts of salivation were observed in 1 placebo control animal, 6 cats in the 1X treatment group, 10 cats in the 3X treatment group, and in 6 cats in the 5X treatment group. All observations of salivation were observed on the day of treatment or the day after treatment except for one observation on day 4 in a 3X treated male cat. There were no treatment-related, biologically-significant effects on body weight, clinical biochemistry, or hematology. Sporadic statistically-significant clinical chemistry and hematology effects were observed in male and female cats in all treatment groups. However, none of the effects are considered toxicologically significant since effects occurred in some control as well as treated animals, no dose-response was observed, and/or measured values were within normal control ranges for cats.

This study is classified as **unacceptable** as supporting data. Due to an increased incidence of salivation, which occurred even at the 1X dose, a 3X to 5X margin of safety was not demonstrated. In addition, the reviewers are concerned about the use of Elizabethan collars in this study, as the cats were unable to groom themselves for 24 hours following application of the test material. Under normal (label specified) application directions, the cats would be able to groom themselves and orally ingest the product immediately following application. It is also noted that the proposed label for this product includes specific directions for treatment of kittens over 12 weeks of age; while the youngest cat in this study was 31 weeks of age.

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

I. MATERIALS

A. TEST MATERIAL: Permalool Plus Flea and Tick Foam

Description: Pressurized foam
Lot/Batch No.: LP101996A
Active Ingredients: MGK-264: 1.00%; ETOC: 0.0997%; Pyrethrins:0.300%; Nylar: 0.125%; Permethrin: 0.199%; Linalool: 0.108%;
Storage Conditions: Stored at ambient temperature and humidity

B. ADMINISTRATION: DERMAL

C. VEHICLE AND/OR POSITIVE CONTROL

Vehicle: Permalool Plus Flea and Tick Foam (Placebo)
Positive control: none

D. TEST ANIMALS

Species: Cat
Breed: Domestic shorthair
Age and weight at study initiation: males: 31 to 37 weeks; 3.6-5.2 kg females: 33 to 38 weeks; 2.4-3.6 kg
Source: Liberty Laboratories, Waverly, NY
Housing: individually in elevated metal cages
Diet: Purina Lab Feline Diet #5003, amount not specified
Water: *ad libitum*
Environmental conditions:
Temperature: 63-79°F
Humidity: 8-56%
Acclimation period: 14 days

II. STUDY DESIGN

A. IN LIFE DATES

Start: October 15, 1996; end: February 14, 1996

B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

Cats were randomly distributed within the experimental groups (Table 1) on the basis of body weight using a random permutation table. Groups of 6 cats/sex were dermally treated with 1) five applications of placebo; or 2) one application (1X) of test material; or 3) three applications (3X) of test material; or 4) five applications (5X) of the test material. For the placebo, 3X and 5X groups, applications were made at one hour intervals. From information on p. 11 of MRID 44314010: "Two males and two females from each dose group {representing a single block (squad) of animals} were dosed on three consecutive days to yield three blocks (squads) of animals."

According to the report text, the test material was applied according to label directions, and "the head was treated with care to avoid the eyes." The animals were not toweled after treatment in order to permit drying of the applied material. Elizabethan collars were applied to the animals for 24 hours following application. Label directions give the following directions for application:

"Cover animal's eyes with a hand. Do not spray directly on mouth, nose and eyes. Spray head, ears and chest until damp. With finger tips, rub into face, around mouth, nose and ears. Then spray from the neck to the tail, finishing legs last. For best penetration of spray to skin and on heavily coated animals, direct spray against the natural lay of the hair, spraying the ruffled hair directly behind the hand. Make sure the spray thoroughly wets ticks. [When used on miniature and toy breeds of dogs or on cats, towel dry the animal after ½ hour if not totally dry.]... Avoid contact with genitalia."

Table 1. Experimental Design

Group	No. of Animals		Treatment	Number of Applications
	Male	Female		
1	6	6	Placebo	5
2	6	6	Test Material	1
3	6	6	Test Material	3
4	6	6	Test Material	5

Data taken from p. 11, MRID 44314010.

C. DOSE SELECTION RATIONALE

The rationale for dose levels was to establish the margin of safety and potential dermal and systemic toxicity of 1X, 3X, and 5X of the recommended topical application.

D. EXPERIMENTAL DESIGN

Clinical observations were conducted hourly for four hours following the final application of test material or placebo and twice daily, thereafter, for 27 days. Effects on skin and fur, eyes and mucous membranes, respiratory system, circulatory system, autonomic and central nervous system, somatomotor activity and behavior pattern were noted. Particular attention was paid to seizures, tremors, salivation, vomiting, and diarrhea. Body weights were recorded pre-test and on days 0, 7, 14, 21, and 28 of the study. Food consumption was measured daily for each animal during the acclimation period and during the study. Food consumption on days -2 and 0 were measured for 6 hour periods due to fasting for clinical chemistry and hematology testing.

E. PATHOLOGICAL PARAMETERS

Blood samples were obtained by venipuncture of the jugular vein on Day -1 (pretreatment) and Day 1. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)*
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)*
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)*
x	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)*		
x	(Activated partial thromboplastin time)*		
	Erythrocyte morphology		

*Recommended in 81-6 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium	x	Blood urea nitrogen*
x	Phosphorus*		Total Cholesterol
x	Potassium*	x	Globulin*
x	Sodium*	x	Glucose*
		x	Total and direct bilirubin*
	ENZYMES	x	Total serum protein*
x	Alkaline phosphatase(ALK)*		(TP)
	Cholinesterase(ChE)		Triglycerides
	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)		
x	Serum alanine amino-transferase (also SGPT)*		
x	Serum aspartate amino-transferase(also SGOT)*		
	Gamma glutamyl transferase(GGT)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in 81-6 Guidelines.

F. STATISTICS

Group mean values with standard deviations were calculated from numerical data. Between day comparisons of mean clinical-chemistry and hematology data within each treatment group were done with a paired two-tailed Student's t-test. Body weight and food consumption data were compared using a one-way ANOVA. If significant ($p \leq 0.05$) differences were found, Bonferroni's Multiple Comparison post-test was used to determine statistical significance.

G. DISPOSITION OF ANIMALS

The cats were returned to the animal colony at White Eagle Laboratories at the end of the study.

H. COMPLIANCE

Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

III. RESULTS

A. EXPOSURE LEVELS

The exact test article exposure concentrations could not be calculated from the information provided. The Flea and Tick Foam was applied according to package

directions. The animals were not toweled after treatment so that the test or control material could air dry.

B. MORTALITY

No cats died during the study.

C. CLINICAL SIGNS

Small to moderate amounts of salivation were observed in 1 placebo control animal, 6 cats (3 males and 3 females) in the 1X treatment group, 10 cats (5 males and 5 females) in the 3X treatment group, and in 6 cats (2 males and 4 females) in the 5X treatment group. All observations of salivation were observed on the day of treatment or the day after treatment except for one observation on day 4 in a 3X treated male cat. Lacrimation was observed in one control female on the day of treatment, in one 3X treated male on the day after treatment, and in one 3X treated female on day 14. Diarrhea was observed in one 1X treated female on day 7 and dermal irritation and hair loss were observed on one 1X treated male on days 21-28. Decreased appetite (no food consumption for 72 hours) was observed on day 4 in one 5X treated male and shedding was observed on one 5X treated female on days 26-28.

D. BODYWEIGHT AND WEIGHT GAIN

No significant differences in group body weight means occurred for animals of either sex at any observation period. The mean body weights of all cats increased during the acclimation period and during the 4 week observation period after treatment.

E. FOOD CONSUMPTION

No significant difference in food consumption occurred for treated or control animals at any time during the study.

F. HEMATOLOGY

No treatment-related, biologically-significant hematological effects were observed. Although there were sporadic incidences of statistically significant hematological effects, there was no dose-response and no biological significance since values were generally within normal ranges for cats.

G. CLINICAL CHEMISTRY

No treatment-related, biologically-significant effects were observed. Although there were sporadic incidences of statistically significant clinical chemistry effects, there was no dose-response and no biological significance since values were generally within normal ranges for cats.

H. NECROPSY FINDINGS

No necropsies were performed.

IV. STUDY AUTHOR'S CONCLUSIONS

The statement is made in the report summary (p. 5) that: "There were no test article-related effects noted during the four-week post-dose observation period. Therefore, the test article is considered nontoxic under the conditions of the study."

V. DISCUSSION

Groups of 6 male and 6 female domestic shorthair cats were treated five times with a placebo control foam or once, 3X or 5X at 1-hr. intervals with Permalool Plus Flea and Tick Foam.

No mortality was observed and there were no treatment-related, biologically-significant effects on body weight, clinical biochemistry, or hematology. Sporadic statistically-significant clinical chemistry and hematology effects were observed in male and female cats in all treatment groups. However, none of the effects are considered toxicologically significant since some effects occurred in control as well as treated animals, no dose-response was observed, and/or measured values were within normal control ranges for cats.

Small to moderate amounts of salivation were observed from 1 placebo control animal, 6 cats in the 1X treatment group, 10 cats in the 3X treatment group, and in 6 cats in the 5X treatment group. All observations of salivation were observed on the day of treatment or the day after treatment except for one observation on day 4 in a 3X treated male cat. In contrast to the conclusions of the study author, the reviewer believes that the tendency towards a dose-response suggests that the salivation may be treatment-related.

This study generally followed the pertinent guidelines for a companion animal safety study (86-1). However, due to the apparent treatment-related salivation which occurred at even the 1X dose, a 3X to 5X margin of safety was not demonstrated. In addition, the reviewers are concerned about the use of Elizabethan collars in this study, as the cats were unable to groom themselves for 24 hours following application of the

proposed product. Under normal (label specified) application directions, the cats would be able to groom themselves and orally ingest the product in the period immediately following application. It is also noted that the proposed use directions for this product include directions for application to kittens of over 12 weeks of age; the youngest cat in this study was 31 weeks old.

Because of the concerns indicated above, the study is classified as **unacceptable**, and it does not support the proposed use of this product on cats.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D246641
2. **PC CODE:** 057001, 109701, 069001, 129032, 128722, 128838
3. **CURRENT DATE:** Sept. 24, 1998
4. **TEST MATERIAL:**

057001 N-Octyl bicycloheptene dicarboximide.....1.000%
109701 Permethrin.....0.199%
069001 Pyrethrins.....0.300%
129032 Pyriproxyfen (Nylar).....0.125%
128722 ETOC.....0.0997
128838 Linalool.....0.108%

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Companion animal safety/dog/ White Eagle Toxicology Laboratories/96668/FEB-4-1997	44314009	No symptoms at 1X, 3X and 5X dosage levels.	-	A
Companion animal safety/ cat/White Eagle Toxicology Laboratories/96667/APR-16-1997	44314010	Increased incidence of salivation following treatment at 1X, 3X and 5X dosage levels. Cats wore Elizabethan collars, preventing grooming (and possible oral ingestion of the test material).	-	U

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**